

REMARKS

I. Status Summary

Claims 1-4, 6-14, 36, 38, 39, and 41-47 are now pending in the subject U.S. patent application and have been examined by the United States Patent and Trademark Office (hereinafter "the Patent Office").

Claims 1-3, 6-9, 36, 38, 39, and 41-47 remain rejected under 35 U.S.C. §103(a) upon the contention that the claims are unpatentable over McMahan *et al.* (1996) 236 *Anal Biochem* 101-106 (hereinafter "McMahan") or the Molecular Probes Technical Literature of record (hereinafter "Molecular Probes") in view of U.S. Patent No. 7,183,392 to Wagner et al. (hereinafter "Wagner"), Chaga *et al.* (2001) 49 *J Biochem Biophys Meth* 49:313-334 (hereinafter "Chaga"), and Zachariou *et al.* (2000) 890 *J Chromatog A* 890:95-116 (hereinafter "Zachariou").

Claims 1, 2, 4, 6-14, and 41-46 also remain rejected under 35 U.S.C. §103(a) upon the contention that the claims are unpatentable over Ehteshami (1996) Synthesis and Characterization of Bioaffinity Interactive Heterobifunctional Polyethylene Glycols, Ph.D. dissertation, University of Arizona (hereinafter "Ehteshami"), as evidenced by Ehteshami *et al.* (1996) 9 *J Mol Recog* 733-737 (hereinafter "Ehteshami et al.") in view of Chaga and Zachariou.

Claims 36, 37-39, and 47 remain rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Ehteshami as evidenced by Ehteshami et al. in view of Chaga and Zachariou, and in further view of Molecular Probes. All rejections were made final in the Official Action dated November 13, 2008.

Claims 1-4, 6-10, 36, and 41-46 have been amended. New claim 48 has been added. Applicant respectfully requests that the amendment to these claims be entered. Support for the amendments can be found throughout the specification as filed, including but not limited to in the specification at page 13, lines 18-21 and at page 25, lines 1-6. Accordingly, no new matter has been added by the amendments to the claims.

Reconsideration of the application as amended and based on the remarks set forth herein below is respectfully requested.

II. Responses to the Rejections under 35 U.S.C. § 103

Claims 1-3, 6-9, 36, 38, 39, and 41-47 stand rejected under 35 U.S.C. §103(a) upon the contention that the claims are unpatentable over McMahan or Molecular Probes in view of Wagner, Chaga, and Zachariou. Claims 1, 2, 4, 6-14, and 41-46 also stand rejected under 35 U.S.C. §103(a) upon the contention that the claims are unpatentable over Ehteshami as evidenced by Ehteshami et al. in view of Chaga and Zachariou. Claims 36, 37-39, and 47 also stand rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Ehteshami as evidenced by Ehteshami et al. in view of Chaga and Zachariou, and in further view of Molecular Probes.

After careful consideration of the rejections and the Patent Office's bases therefor, applicant respectfully traverses the rejections and submit the following remarks.

II.A. Response to the First Obviousness Rejection

Claims 1-3, 6-9, 36, 38, 39, and 41-47 stand rejected under 35 U.S.C. §103(a) upon the contention that the claims are unpatentable over McMahan or Molecular Probes in view of Wagner, Chaga, and Zachariou. The Patent Office contends that McMahan discloses a conjugate comprising an NTA polydentate chelator and a biotin detectable moiety conjugated to the polydentate chelator. The chelator is asserted to be conjugated to Ni^{2+} . Molecular Probes is asserted to disclose a conjugate of the formula Biotin-X NTA comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety (again, with Ni^{2+} as the chelator). The Patent Office concedes, however, that neither McMahan nor Molecular Probes teaches that the chelated metal ion is Fe^{3+} , Al^{3+} , Yb^{3+} , or Ga^{3+} .

Wagner is asserted to teach nitrilotriacetic acid coordinated with metals such as Ni, Co, Fe, and Cu bind His-tags of from 6 to 9 amino acids. Chaga is asserted to teach IMAC as a separation technique that utilizes the differential affinity of proteins for immobilized metals to effect their separation, wherein hard metals such as Fe^{3+} , Ca^{2+} , Al^{3+} show preference for oxygen, soft metals such as Cu^{+} and Hg^{2+} prefer sulfur, and intermediate metals such as Cu^{2+} , Ni^{2+} , Zn^{2+} , and Co^{2+} coordinate to nitrogen, oxygen, and sulfur. Chaga is also asserted to teach that IMAC has seen extensive work in the

purification of proteins from complex biological samples such as the use of Cu^{2+} , Ni^{2+} , and Zn^{2+} for the purification of proteins having exposed histidine residues, as well as the use of Fe^{3+} and Ga^{3+} for the enrichment of phosphorylated proteins and peptides. Additionally, the reference is asserted to teach that immobilized Fe^{3+} would adsorb a distinct profile of proteins at acidic pH from that which would be adsorbed to immobilized Cu^{2+} at neutral pH. Zachariou is asserted to teach the binding properties of immobilized O-phosphoserine (*im-OPS*) and 8-hydroxyquinoline (*im-8-HQ*) with immobilized iminodiacetic acid (IDA) as the control system in combination with the hard Lewis metal ions, Al^{3+} , Ca^{2+} , Fe^{3+} , Yb^{3+} , and the borderline metal ion Cu^{2+} , over a pH range of 5.5 to 8.0. With regards to the pH, the reference is asserted to teach that with an incubation/equilibrium buffer of 0.5 M or 0.06M ionic strength, fewer proteins bound to these hard Lewis metal ion IMAC adsorbents as the pH became increasingly alkaline, opposite to what is observed with protein with the borderline Lewis metal ion IMAC systems.

From this, the Patent Office asserts that it would have been *prima facie* obvious to one of skill in the art to combine the teachings of the cited references to modify the heterobifunctional conjugate as assertedly taught by McMahan or Molecular Probes with Fe^{3+} in view of the asserted teachings of Wagner. According to the Patent Office, one would have been motivated to do so because Wagner teaches that NTA coordinated with Fe^{3+} binds His-Tags. Thus, it is contended that one of ordinary skill in the art would have a reasonable expectation of success that by modifying the heterobifunctional conjugate as taught by McMahan or Molecular Probes with Fe^{3+} in view of the teachings of Wagner one would achieve a metal chelate which recognizes a His tag.

The Patent Office further contends that it would have been *prima facie* obvious to combine the teachings of the references so as to substitute the metal ion which coordinates to the heterobifunctional conjugate as taught by McMahan or Molecular Probes to a hard Lewis metal ion such as Fe^{3+} , Al^{3+} , Yb^{3+} , or Ga^{3+} upon the contention that Chaga teaches that different metals such as hard Lewis metals may be successfully used for detecting various proteins such as phosphoproteins which are not detected using intermediate metals such as Cu^{2+} , Ni^{2+} , Zn^{2+} , or Co^{2+} .

And finally, the Patent Office asserts that it would have been *prima facie* obvious to combine the teachings of the references so as to use a lower pH binding solution when detecting proteins using hard Lewis metal ions such as Fe^{3+} , Al^{3+} , Yb^{3+} , or Ga^{3+} because it is asserted that the prior art recognizes as taught by both Chaga and Wagner, that hard Lewis metals preferentially bind proteins at a lower pH than intermediate metals such as Cu^{2+} , Ni^{2+} , Zn^{2+} , and Co^{2+} .

Initially, without acquiescing to the contentions of the Patent Office, claim 1 has been amended to recite *inter alia* a composition comprising a membrane having bound phosphoprotein, wherein the phosphoprotein is coordinated to a phosphoprotein detection reagent (PPDR). Claims 36, 41, and 46 have been similarly amended.

Applicant respectfully submits that the Patent Office has not presented a *prima facie* case of unpatentability of the present claims over the cited references. Applicant respectfully traverses the Patent Office's assertion that one of ordinary skill in the art would have been motivated to modify the heterobifunctional conjugates of McMahan or Molecular Probes with Fe^{3+} in view of the teachings of Wagner because Wagner is asserted to teach that NTA coordinated with Fe^{3+} binds His-Tags. Both McMahan and Molecular Probes at best appear to teach using Ni^{2+} for binding His-Tags.

Further, applicant respectfully directs the attention of the Patent Office to MPEP § 2143.01, which states in part:

V.THE PROPOSED MODIFICATION CANNOT RENDER THE PRIOR ART UNSATISFACTORY FOR ITS INTENDED PURPOSE

If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984) (Claimed device was a blood filter assembly for use during medical procedures wherein both the inlet and outlet for the blood were located at the bottom end of the filter assembly, and wherein a gas vent was present at the top of the filter assembly. The prior art reference taught a liquid strainer for removing dirt and water from gasoline and other light oils wherein the inlet and outlet were at the top of the device, and wherein a pet-cock (stopcock) was located at the bottom of the device for periodically removing the collected dirt and water. The reference further taught that the separation is assisted by gravity. The Board concluded the claims were *prima facie* obvious, reasoning that it would have been obvious to turn the reference device upside

down. The court reversed, finding that if the prior art device was turned upside down it would be inoperable for its intended purpose because the gasoline to be filtered would be trapped at the top, the water and heavier oils sought to be separated would flow out of the outlet instead of the purified gasoline, and the screen would become clogged.).

In the instant rejection, the cited art involves solid phase affinity chromatography. The references employ detection of His-tags located on the end of proteins, because the His-tags must be accessible to the chelator for the solid phase affinity chromatography to be successful. By contrast, the subject matter of the instant application and present claims is directed to detection of phosphorylated amino acids within the protein's sequence, rather than on the end, and utilizing a membrane for immobilization.

MPEP § 2143.01, cited above, counsels against arriving at the asserted combination, because the modifications and rearrangements required of the cited art to practice the subject matter of the instant invention, involving *inter alia* entirely different placement of the chelator, are tantamount to turning the device or composition "upside down," as in *In re Gordon*. As such, the modifications would render the prior art references "unsatisfactory for the intended purpose."

McMahan, Molecular Probes, Wagner, and Chaga all at best appear to teach methods related to detection of His-tags, whereas the instant claims are drawn to detection of phosphate groups. Applicant respectfully submits that Zachariou also fails to cure this deficiency. As disclosed in Zachariou at, for example, page 96 (left column, first full paragraph) *im*-OPS is employed as a chelator moiety. Applicant respectfully submits that Zachariou's disclosure as to how *im*-OPS might behave as a chelator provides no information as to how a chelated metal ion might interact with a phosphoprotein.

Moreover, in *KSR*, the Supreme Court stated:

[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new

invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and *claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.*

KSR International Co. v. Teleflex Inc., 82 USPQ 2d 1385, 1396 (U.S. 2007) (emphasis added).

Thus, while more than two documents clearly may be combined to form the basis of a rejection under 35 U.S.C. § 103(a), the U.S. Supreme Court appears to have indicated that a common sense approach should be employed for determining whether claims are obvious. In view of this language, it seems that combining numerous documents to arrive at the claimed subject matter as a whole and still failing to meet all of the elements claimed (such as detection of phosphoprotein using a membrane for immobility) points to patentability of the instant subject matter over the cited references.

Applicant respectfully submits that the asserted combination of prior art references impermissibly employs hindsight to arrive at obviousness conclusions where the prior art guidance is, at best, so minimal as indicated above. The references do not suggest detection of phosphate groups, and the arrangement of any commonly employed elements is so different that the cited combination fails to suggest the claimed subject matter to one skilled in the art.

Claims 1, 36, 41 and 46 are believed to be patentably distinguished over the cited art. By virtue of their dependency from claims 1, 36, and 41, respectively, claims 2-4, 6-9, 38, 39, 42-45, and 47 are also believed to be distinguished from the cited references.

Summarily, applicant respectfully submits that the Patent Office has not presented a *prima facie* case of unpatentability of claims 1-3, 6-9, 36, 38, 39, and 41-47 over McMahan or Molecular Probes in view of Wagner, Chaga, and Zachariou. As such, applicant respectfully requests that the instant rejection be withdrawn at this time.

II.B. Response to the Second Obviousness Rejection

Claims 1, 2, 4, 6-14, and 41-46 also stand rejected under 35 U.S.C. §103(a) upon the contention that the claims are unpatentable over Ehteshami, as evidenced by Ehteshami et al. in view of Chaga and Zachariou. According to the Patent Office, Ehteshami discloses a conjugate comprising IDA as a polydentate chelator moiety and

a biotin detectable moiety conjugated to the IDA moiety via a PEG spacer group. The reference is also asserted to teach a method of synthesizing the conjugate, and as evidenced by Ehteshami et al., that the composition is soluble in aqueous solution.

As such, the Patent Office asserts that Ehteshami teaches a heterobifunctional conjugate comprising a polydentate chelator, a linker, and a detectable moiety. The Patent Office concedes, however, that Ehteshami does not teach that the metal ion is Fe^{3+} , Al^{3+} , Yb^{3+} , or Ga^{3+} . These deficiencies are asserted to be cured by Chaga and Zachariou discussed hereinabove.

Initially, without acquiescing to the contentions of the Patent Office, claim 1 has been amended to recite *inter alia* a composition comprising a membrane having bound phosphoprotein, wherein the phosphoprotein is coordinated to a phosphoprotein detection reagent (PPDR). Claims 10, 41, and 46 have been similarly amended.

Applicant respectfully submits that Ehteshami as evidenced by Ehteshami et al. in view of Chaga and Zachariou fails to support a rejection of claims 1, 2, 4, 6-14, and 41-46 under 35 U.S.C. § 103(a). Applicant respectfully submits that the deficiencies discussed hereinabove with respect to Chaga and Zachariou are equally present in the instant combination of references. Therefore, applicant respectfully submits that Ehteshami as evidenced by Ehteshami et al. in view of Chaga and Zachariou fails to support a *prima facie* case of unpatentability of claim 1 under 35 U.S.C. § 103(a).

The additional arguments above with respect to *In re Gordon* and *KSR* are also believed to be applicable to the instant rejection. As a result, applicant respectfully requests that the instant rejection of claims 1, 2, 4, 6-14, and 41-46 be withdrawn at this time.

II.C. Response to the Third Obviousness Rejection

Claims 36, 37-39, and 47 have also been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Ehteshami as evidenced by Ehteshami et al. in view of Chaga and Zachariou, and in further view of Molecular Probes.

With respect to the instant rejection, applicant respectfully submits that Ehteshami as evidenced by Ehteshami et al. in view of Chaga and Zachariou does not disclose or suggest the subject matter of present claim 36 for the reasons set forth

hereinabove. Applicant further respectfully submits that Molecular Probes does not cure the deficiencies discussed hereinabove.

Therefore, applicant respectfully submits that the combination of Ehteshami as evidenced by Ehteshami et al. in view of Chaga and Zachariou, and in further view of Molecular Probes fails to support a rejection of claims 36, 37-39, and 47 under 35 U.S.C. § 103(a). As a result, applicant respectfully requests that the instant rejection be withdrawn at this time.

III. Discussion of New Claim

New claim 48 has been added, and is dependent on claim 1. Support for claim 48 can be found in claim 1 as previously presented, among other places. No new matter has been added. New claim 48 is believed to be in condition for allowance for at least the reasons set forth herein above with respect to claim 1.

CONCLUSIONS

In accordance with the amendments to the claims and the remarks presented hereinabove, applicant respectfully submits that claims 1-4, 6-14, 36, 38, 39, and 41-47 are in condition for allowance, and respectfully solicits a Notice of Allowance to that effect.

Should there be any minor issues outstanding in this matter, Examiner Fetterolf is respectfully requested to telephone the undersigned attorney. Early passage of the subject application to issue is earnestly solicited.

Deposit Account

The Commissioner is hereby authorized to charge any deficiency in payment or credit any overpayment associated with the filing of this correspondence to Deposit Account Number 50-0426.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: August 7, 2009

By: _____



Arles A. Taylor, Jr.
Registration No. 39,395
Customer No. 25297
(919) 493-8000

421/73/2 AAT/MCG/cam